III. REMARKS

Reconsideration of the present application as amended is respectfully requested.

Reconsideration of this application in view of the following remarks is respectfully requested. Claims 1, 3, 8-10, 12-27, 29-32, and 35-45 are currently pending. Claims 1, 8-10, 19, 20, 26, 27, 29-31, and 35-41 have been amended without prejudice. It is respectfully submitted that no new matter has been added by virtue of the present amendment.

A. Objection

Claims 19, 20 and 27 were objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner notes that "[e]ach of these claims depend from claim 1 and require a sustained release carrier that releases the opioid agonist over a time period of about 8 to about 24 hours", and that this is already required in claim 1.

In response, it is noted that claims 19, 20 and 27 (which now depend from claim 8) recite that (i) the antagonist is in sustained release form, (ii) the acetaminophen is in sustained release form and (iii) the antagonist and the acetaminophen are in sustained release form, respectively, with the particular limitations of the claims. It is respectfully submitted that these dependent claims do further limit claim 8 (and previous claim 1) which recited that the opioid agonist is released over a time period of about 8 to about 24 hours. Therefore, the Examiner is requested to remove this objection.

B. Rejection under 35 U.S.C. § 112

Claims 29-30 were rejected under 35 U.S.C., second paragraph, as being indefinite. The Examiner stated that "claims 29-30 depend from canceled claim 28 are therefore indefinite since they are incomplete."

In response, claim 29 has been amended to depend from claim 1, and claim 30 depends from claim 29. Therefore, the Examiner is respectfully requested to remove this rejection.

C. **Rejection under 35 U.S.C. § 103(a) over Crain in combination with the Physicians Desk Reference and Oshlack**

Claims 1, 3, 6, 8-32 and 34-40 were rejected under 35 U.S.C. 103(a) "as being unpatentable over Crain et al (5,512,578; hereafter '578) in combination with the Physicians Desk Reference for either Vicodin, Lorcet or Lortab (1995; hereafter PDR) and further in combination with Oshlack et al (U.S. Pat. No. 5,472,712; hereafter '712)."

The Examiner states that "it would have been obvious to one skilled in the art at the time of the invention to include non-narcotic analgesics in the formulation of '578 in an effort to provide enhanced analgesia by means of producing analgesia though (sic) non-opioid antinociceptive pathways." The Examiner further states that "it would have been obvious to one skilled in the art at the time of the invention to use an opioid dose that would otherwise be subtherapeutic if given alone with the motivation of maintaining low instance of side effect while maintaining an analgesic effectiveness," and "it would also have been obvious to one skilled in the art at the time of the invention to provide controlled release formulations of the obvious previous compositions to reduce the frequency of administration."

In order to expedite allowance of the claims, independent claim 1 has been amended, in pertinent part, to recite "the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but which (i) is aversive in physically dependent human subjects when administered in the same amount and in a higher amount than said therapeutically effective amount; and (ii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist together with the acetaminophen relative to the same therapeutic amount of opioid analgesic together with the acetaminophen when administered to human patients without said opioid antagonist."

With respect to Crain et al., Applicants note that Crain et al. is directed to a method of selectively enhancing the analgesic potency of morphine and other clinically used bimodally-acting opioid agonists and simultaneously attenuating development of physical dependence, tolerance and other undesirable side effects. Even when comparing the closest ratios provided in the present case as compared to Crain et al., the amount of antagonist which would be included in the formulations and methods of the present invention would be at least three times the amount of antagonist as Crain et al. (0.03:1 as compared to 0.01:1). In order to attain the presently claimed parameters, one would administer orally effective dose of an opioid agonist/acetaminophen combination (e.g., in mg amounts) together with an antagonist in an amount which would provide the claimed effects. In contrast, Crain et al. appears to be directed to combinations of opioid agonists and opioid antagonists wherein the antagonists are administered at ultra-low doses (e.g., about 1 microgram (see Crain '578 at column 5, lines 35-40 and column 6, lines 60-65); or pM concentrations (see Crain '578 at column 8, lines 41-63 and column 9, lines 35-41)). Consequently, in Crain et al. the opioid agonists may be administered at, e.g., 10-100 times lower doses than when administered alone. (see Crain '578 at column 6, lines 44-65 and column 8, lines 40-62).

In summary, Crain '578 desires enhanced analgesic potency resulting from the inclusion of the antagonist; which is not a goal of the present claims and which is excluded via the present claims. Crain '578 desires simultaneous attenuation of the development of physical dependence; in contrast, the present invention is geared to precipitating an aversive response in a physically dependent patient. Thus, Crain '578 desires to avoid the possibility of its formulations causing addiction, whereas the present invention prevents abuse of its analgesic formulations by addicts.

It is respectfully submitted that the Physicians Desk Reference and Oshlack et al fail to cure the deficiencies of Crain et al. described above, and it is respectfully submitted that none of the combination of references cited by the Examiner teach, hint or suggest the presently claimed invention.

Therefore, the Examiner is respectfully requested to remove this rejection.

D. Rejection under 35 U.S.C. § 103(a) over Gordon in combination with the Physicians Desk Reference and Oshlack

Claims 1, 3, 6, 8-32, 34-40 were rejected under 35 U.S.C. 103(a) "as being unpatentable over Gordon et al (4,457,933, hereafter '933) in combination with the Physicians Desk Reference for either Vicodin, Lorcet or Lortab (1995; hereafter PDR) and further in combination with Oshlack et al (5,472,712; hereafter '712).

The Examiner states that "it would have been obvious to one skilled in the art at the time of the invention to include non-narcotic analgesic in the formulation of '578 (sic) in an effort to provide enhanced analgesia by means of producing analgesia though (sic) non-opioid antinocicpetive pathways." The Examiner further states that "it would have been obvious to one skilled in the art at the time of the invention to use an opioid dose that would otherwise be subtherapeutic if given alone with the motivation of maintaining low instance of side effect while maintaining an analgesic effectiveness," and "it would also have been obvious to one skilled in the art at the time of the invention to provide controlled release formulations of the obvious previous compositions to reduce the frequency of administration."

In order to expedite allowance of the claims, independent claim 1 has been amended, in pertinent part, to recite "the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but which (i) is aversive in physically dependent human subjects when administered in the same amount and in a higher amount than said therapeutically effective amount; and (ii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist together with the acetaminophen relative to the same therapeutic amount of opioid analgesic together with the acetaminophen when administered to human patients without said opioid antagonist."

With respect to Gordon et al., it is respectfully submitted that Gordon et al. purportedly "concerns a method for decreasing both the oral and parenteral abuse potential of strong analgetic agents, such as oxycodone, propoxyphene and pentazocine by combining an analgesic dose of the analgetic agents with naloxone in specific, relatively narrow ranges." *See, e.g.,* Abstract of Gordon et al. It is respectfully submitted that Gordon et al. fails to teach, hint, or suggest, "a combination product which is analgesically effective when the combination is administered orally, but which is aversive in physically dependent human subjects . . . ." as recited in claim 1 of the present invention.

It is respectfully submitted that the Physicians Desk Reference and Oshlack et al fail to cure the deficiencies of Gordon et al. described above, and it is respectfully submitted that none of the combination of references cited by the Examiner teach, hint or suggest the presently claimed invention. It is respectfully submitted that none of the combination of references cited by the Examiner teach or suggest the presently claimed invention.

Therefore, the Examiner is respectfully requested to remove this rejection.

E. Rejection under 35 U.S.C. § 103(a) over Crain et al. in view of the Physician Desk Reference or Gordon et al. in combination with the Physicians Desk Reference

Claim 41 was rejected under 35 U.S.C. 103(a) "as being unpatentable over Crain et al (5,512,578; hereafter '578) in view of the Physicians Desk Reference for either Vicodin, Lorcet, or Lortab (1995; hereafter PDR) OR Gordon et al (4,457,933; hereafter '933) in combination with the Physicians Desk Reference for either Vicodin, Lorcet or Lortab (1995; hereafter PDR)."

In response, claim 41, now recites "the dosage form having a ratio of opioid antagonist to opioid agonist to acetaminophen that provides a combination product which is analgesically effective when the combination is administered orally, but which (i) is aversive in physically dependent human subjects when administered in the same amount as said therapeutically

effective amount; and (ii) maintains an analgesic effect but does not increase analgesic efficacy of the opioid agonist together with the acetaminophen relative to the same therapeutic amount of opioid analgesic together with the acetaminophen when administered to human patients without said opioid antagonist."

As Crain et al. and Gordon et al. fail to teach, hint, or suggest "a combination product which is analgesically effective when the combination is administered orally, but which (i) is aversive in physically dependent human subjects when administered in the same amount as said therapeutically effective amount . . ." and the Physicians Desk Reference fails to cure the deficiencies of Crain et al. and Gordon et al., the Examiner is respectfully requested to remove this rejection.

III. Double Patenting Rejection of Claims 1-36.

In the Office Action, claims 1, 3, 8-10, 12-27, 29-32, and 35-41 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-50 of U.S. Patent No. 6,277,384.

In addition, claims 1, 3, 6-32, and 34-40 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of copending Application No. 09/503,020.

In response, Applicants will consider the filing of Terminal Disclaimers to obviate the double-patenting rejections upon indication from the Examiner that the claims are otherwise allowable.

IV. Conclusion

It is now believed that the above-referenced rejections and objections have been obviated and it is respectfully requested that the rejections and objections be withdrawn. It is believed that all claims are now in condition for allowance.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: Robert J Paradiso
Robert J. Paradiso
Reg. No. 41,240

by David G Gaskey
Reg No. 45,991

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940